PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#7

Applicant	:	John A. Arcadi
Application No.	:	09/383,114
Filed	:	August 25, 1999
Title	:	COMPOSITION AND METHOD FOR TREATING PROSTATE CANCER
Grp./Div.	:	1614
Examiner	:	J. Goldberg
Docket No.	:	35687/RWJ/H29

DECLARATION

Assistant Commissioner for Patents
Washington, D.C. 20231

Post Office Box 7068
Pasadena, CA 91109-7068

Commissioner:

I, Lawrence W. Jones, declare that:

1. I am a licensed physician in the State of California, and the Director of Prostate Research Program at Huntington Medical Research Institutes (HMRI), the assignee of this patent application.

2. This patent application covers the use of Rhodamine-123 for treating hormone-refractory prostate cancer, which kills 40,000 men annually in the United States. Prior to this invention, there was no known life-prolonging treatment for this disease.

HMRI filed with the U.S. Food and Drug Administration (FDA) an Investigational New Drug Phase I Application, which was approved for the experimental testing of Rhodamine-123 to treat human prostate cancer *in vivo*. Clinical testing to determine a safe dosage level of Rhodamine-123 for humans began under my supervision as Principal Investigator on February 1, 1999. Under Phase I of the approved protocol, 27 volunteer patients are to be treated in nine groups of three each, with each volunteer receiving a single dose of Rhodamine-123.

3. Once the current study has been completed, volunteers will thereafter be treated with multiple doses of Rhodamine-123, starting at a dosage that has been established as non-toxic.

4. We have completed infusion of 12 volunteers with Rhodamine-123 and have data showing the percentage change of prostate specific antigen (PSA) two weeks after infusion. Prior to treatment, each volunteer was diagnosed as having hormone-refractory prostate cancer (HRPC), which usually leads to death within about two years after the onset of the condition. Each volunteer was treated in accordance with protocol approved by the FDA. The attached graph shows the PSA change for each volunteer two weeks after infusion with Rhodamine-123. To date, no sign of toxicity has been observed in any of the volunteers tested.

5. As indicated on the attached graph, volunteers 1, 2 and 3 were each infused with 0.3mg of Rhodamine-123 per kg of patient body weight (0.3mg/kg). Volunteers 4, 5 and 6 were each infused with a dose of 0.6mg/kg. Volunteers 7, 8 and 9 were each infused with a dose of 1.2mg/kg, and volunteers 10, 11 and 12 each received 2.4mg/kg.

6. As shown in the accompanying graph, volunteers 3, 4, 8 and 12 each experienced a substantial decrease in PSA. The drop exceeded 50% for volunteers 8 and 12. This is important because Kantoff, P.W., et al. reported in the *Journal of Clinical Oncology*, Vol. 17, No. 8 (August), 1999:pp 2506-2513, at page 2509 that median survival time for patients with hormone refractory prostate cancer (HRPC) is significantly extended if a patient has a 50% or greater drop in PSA level after treatment. A copy of the Kantoff, P.W., et al. paper is enclosed.

7. Although the results to date must be considered only preliminary, they are encouraging because of the significant reduction of PSA levels in some of the patients, although each patient received only one dose of a relatively small amount of Rhodamine-123. Moreover, volunteer 12 entered the study with lower limb edema. This had been diagnosed as due to lymphatic obstruction by a tumor in the pelvis of the patient. When seen by the physician one month after treatment with Rhodamine-123 as referred to above, the edema was almost absent, suggesting a possible reduction in tumor mass.

8. We are continuing clinical testing under Phase I of the approved protocol. Once dose-limiting toxicity has been obtained with a single dose of Rhodamine-123, subsequent volunteers will each be treated with multiple doses of Rhodamine-123 at the maximum tolerated dose. That will complete Phase I of the investigation, and should provide further evidence of the efficacy of the treatment.

9. It is difficult to estimate when clinical testing will be completed, but based on past experience, it is not likely to be done before the end of 2001. The clinical trials and time spent over which they are run depend on the rate at which qualified volunteers can be found and enrolled in the program in accordance with the approved protocol.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date 2/23/2001 By _____
Lawrence W. Jones, M.D.

Enclosures: Graph
Kantoff, P.W., et al. publication

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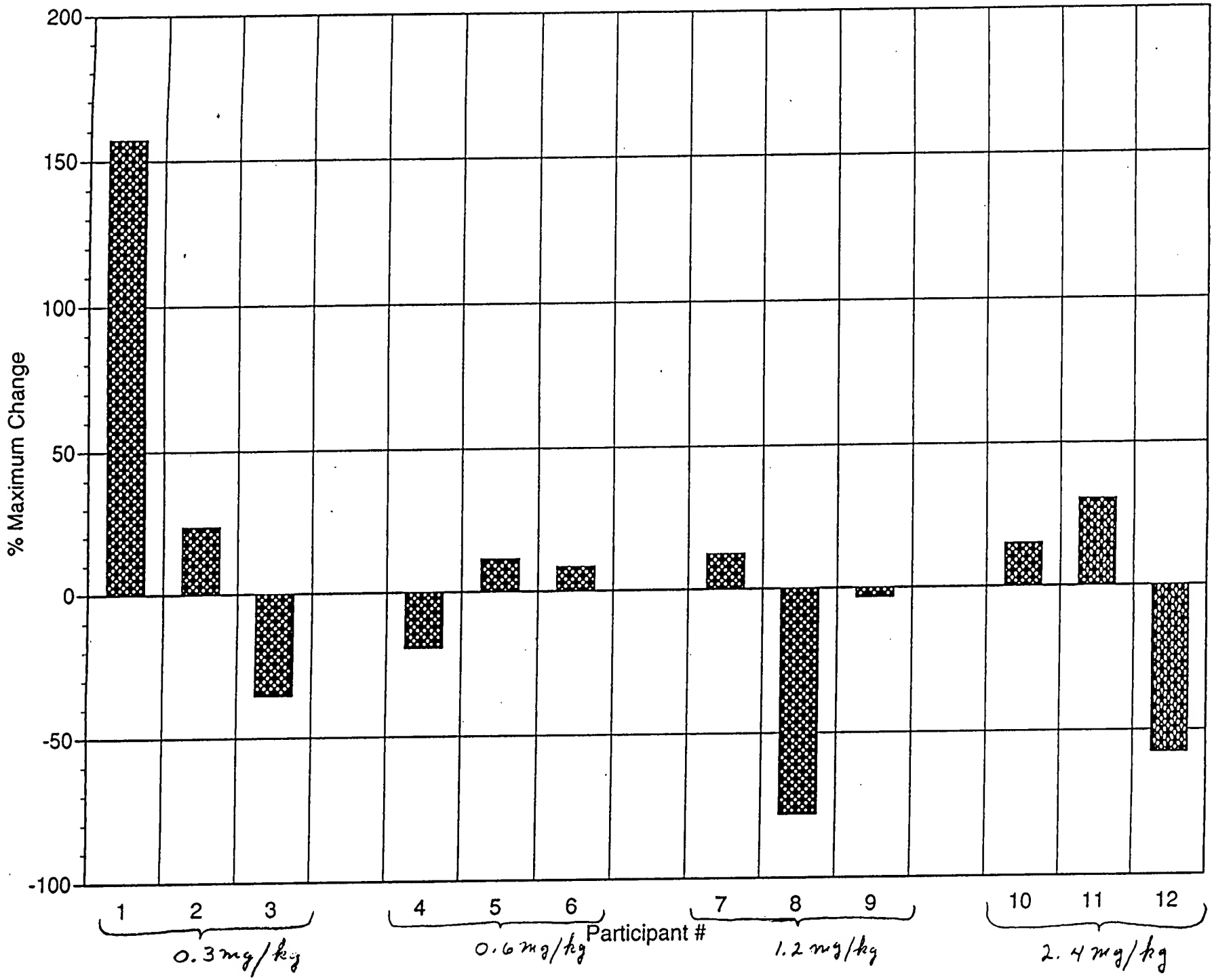
200
150
100
50
0
-50
-100
% Maximum Change
1
2
3
4
5
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7
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9
10
11
12
Participant #
0.3 mg/kg
0.6 mg/kg
1.2 mg/kg
2.4 mg/kg

Hydrocortisone With or Without Mitoxantrone in Men With Hormone-Refractory Prostate Cancer: Results of the Cancer and Leukemia Group B 9182 Study

By Philip W. Kantoff, Susan Halabi, Mark Conaway, Joel Picus, Jeffrey Kirshner, Vera Hars, Donald Trump, Eric P. Winer, and Nicholas J. Vogelzang

Purpose: Approximately 40,000 men die each year of hormone-refractory prostate cancer (HRPC). The results of treatment with chemotherapy have been disappointing to date, with no trials demonstrating a benefit with respect to survival duration. Corticosteroids and mitoxantrone each have been shown to be active agents in this disease. The purpose of this study was to demonstrate an advantage of mitoxantrone and hydrocortisone (M+H) over hydrocortisone alone with respect to survival duration.

Patients and Methods: Two hundred forty-two patients with HRPC were randomized to receive either M+H or hydrocortisone alone. Patients were monitored for survival, time to disease progression, time to treatment failure, response, and quality-of-life (QOL) parameters.

Results: Treatment in both arms was well tolerated. Although there was a delay in time to treatment failure and disease progression in favor of M+H over hydrocortisone alone, there was no difference in overall survival (12.3 months for M+H v 12.6 months for hydrocortisone alone). There was an indication that QOL was better with M+H, in particular with respect to pain control.

Conclusion: M+H generated more frequent responses and a delay in both time to treatment failure and disease progression compared with hydrocortisone alone. In addition, there was a possible benefit of M+H with respect to pain control over hydrocortisone alone. No improvement in survival was observed. Although M+H could be viewed as a palliative option for patients with HRPC, new drugs and novel strategies are needed to improve survival for this disease.

J Clin Oncol 17:2506-2513. © 1999 by American Society of Clinical Oncology.

PROSTATE CANCER IS the most commonly diagnosed malignancy in men. Although many men are cured with treatment, approximately 40,000 men in the United States die of this disease annually.[1] Androgen withdrawal therapy remains the mainstay of treatment for men with advanced disease. When tumors become refractory to androgen withdrawal therapy, further systemic treatment has been of only modest benefit. Chemotherapy has had an undefined impact on the survival duration and quality of life (QOL) of patients. The few randomized clinical trials using chemotherapy usually have been underpowered to detect small differences in outcome.[2] Perhaps more importantly, the agents used in such clinical trials have possessed only marginal activity.

Corticosteroids may act in a variety of ways in men with prostate cancer. As a treatment strategy, corticosteroids represent a minimally toxic, low-cost therapy with some activity against prostate cancer and with an apparent beneficial effect on QOL.[3] Mitoxantrone is an anthracenedione that has demonstrated activity in a variety of malignancies, including prostate cancer.[4,5] It is a drug that is well suited for the population of men with advanced prostate cancer because it causes relatively modest toxicity. In 1992, the Cancer and Leukemia Group B (CALGB) approved a trial, CALGB 9182, to compare hydrocortisone alone to hydrocortisone plus mitoxantrone (M+H). The primary end point of this study was survival duration. The results are reported here.

PATIENTS AND METHODS

Study Design

Patients were eligible for CALGB 9182 if they had metastatic prostate cancer and had undergone no more than one prior endocrine manipulation. Patients were required to have adequate hepatic, renal, and bone marrow function. Continued use of luteinizing hormone–releasing hormone agonist was required for those who had not undergone an orchiectomy. Antiandrogen withdrawal and subsequent documented disease progression was required before entry soon after the trial was opened. When the trial was activated (June 1992), two

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stratification factors were used: performance status (0 to 1 v 2) and disease status (measurable v assessable). After 60 patients were accrued, the eligibility criteria were changed to allow entry of patients who had undergone more than one prior endocrine manipulation, and a third stratification factor was added: the number of prior endocrine manipulations (1 v ≥ 2). The study was not blinded; patients and physicians knew the treatment assignment. Hydrocortisone was administered orally at a dose of 30 mg in the morning and 10 mg in the evening, and mitoxantrone was administered by intravenous injection at a dose of 14 mg/m^2 every 3 weeks. Dose modifications were mandated for hematopoietic toxicity. Use of growth factors was discouraged. Patients in the hydrocortisone-alone arm were not permitted to cross over to mitoxantrone or doxorubicin. However, alternative chemotherapy was permitted after disease progression in either treatment arm.

From October 1992 to September 1995, 242 patients were registered onto CALGB 9182, with 119 randomized to receive M+H and 123 patients randomized to receive hydrocortisone alone. Four patients, two in each of the treatment arms, never started treatment. Four patients, one in the M+H arm and three in the hydrocortisone-alone arm were ruled ineligible; one patient did not have prostate cancer, one had too low a platelet count, one had too low a hemoglobin level, and one had too high a platelet count. All four of these patients were included in the survival analysis.

The study was designed to detect a 50% increase in survival duration with M+H compared with hydrocortisone alone. Sample size calculations were based on having adequate power (80%) to detect a difference in survival duration under the assumption that the median survival duration in the population of patients who received hydrocortisone alone would be 12 months, compared with 18 months for patients treated with M+H. The expanded eligibility (ie, including patients with more than one prior endocrine manipulation) allowed for patients with potentially poorer prognosis to be entered onto the study, and the sample calculations were amended accordingly but were still based on having 80% power to detect a difference for a hazards ratio of 1.5. Allowing for a 5% ineligibility rate and with a 2-year follow-up period after the accrual period, the target accrual was set at 232 patients. The study closed on September 15, 1995, with a final accrual of 242 patients.

End Points

The primary end point was survival duration, which was defined as the time between randomization and death. For living patients, the survival time was censored at the time of last follow-up. The secondary end points were time to disease progression, time to treatment failure, best response, measures of QOL, and decrease in serum prostate-specific antigen (PSA). The study required serum PSA determinations every 3 weeks and a bone scan every 2 months for the first 4 months, and then every 3 months thereafter. Other scans were mandated by the presence of measurable disease and were performed every 2 months. Patients were evaluated for best response in one of three categories: measurable disease, assessable disease, or bone-only disease. In all categories, a complete response (CR) was defined as disappearance of all disease by scans and normalization (≤ 4 ng/mL) of serum PSA, both of which needed to be sustained for ≥ 28 days. For patients with measurable disease, a partial response (PR) was defined as a ≥ 50% reduction in bidimensional measurable disease for ≥ 4 weeks or a ≥ 80% reduction in serum PSA for ≥ 6 weeks. For patients with assessable and bone-only disease, PR was defined as a more than 80% reduction in serum PSA sustained for ≥ 6 weeks. The criteria for decrease in serum PSA were arbitrarily defined in the protocol as ≥ 50% and ≥ 80% reduction of serum PSA from baseline at a follow-up examination anytime between 4 and 8 weeks. Because this definition did not consider the delayed time to maximum serum PSA decrease in a significant proportion of patients, a post hoc analysis was performed in which the maximum serum PSA decrease (≥ 50% and ≥ 80%) was determined in each arm, including maximum serum PSA decreases achieved beyond 56 days. Stable disease was defined as per National Prostate Cancer Project criteria.

Monitoring and Statistical Methods

The study was monitored by the CALGB Data Safety Monitoring Board. The Lan and Demets analog of the O'Brien-Fleming sequential boundary was used to maintain an overall alpha significance level of 0.05 while conducting interim analyses of this study.[6] CALGB Data Management Center personnel were responsible for quality assurance of all data submitted by the participating institutions.

Fisher's exact, Pearson's χ^2, and the Kruskal-Wallis tests were used to compare treatment arms on demographic and clinical variables. The Kaplan-Meier product-limit estimator was used to estimate the survival duration, time to disease progression, and time to treatment failure in the two arms.[7] The log-rank test was used to compare the treatment arms with respect to survival duration, time to disease progression, and time to treatment failure.[8] The proportional hazards model was used to assess important factors for predicting survival time.[9] The variables included in the model were age (years), race (white v other), treatment arm (M+H v hydrocortisone alone), baseline performance status (1+ v 0), baseline alkaline phosphatase level (≥ 165 U/L v < 165 U/L), baseline lactate dehydrogenase level (≥ 227 U/L v < 227 U/L), baseline hemoglobin level (≥ 13 g/dL v < 13 g/dL), weight loss in the previous 6 months (1% to 5% v none and ≥ 5% v none), measurable disease (yes v no), previous surgery (yes v no), previous radiotherapy (yes v no), prostatectomy (yes v no), orchiectomy (yes v no), and pretreatment serum PSA level (≥ 150 ng/mL v < 150 ng/mL). The serum PSA measurements were transformed on a logarithmic scale. In addition, repeated measures models[10] were used to compare the arms with respect to ln (PSA) profiles and 14 QOL outcomes over time. All tests were performed using a two-sided alpha value of 0.05.

Treatment Failure

Treatment failure was defined as disease progression, appearance of unacceptable toxicity, or patient refusal to continue therapy. Disease progression was defined as worsening performance status of ≥ 1 or the appearance of two or more new lesions on bone scan, or an increase of serum PSA level ≥ 100% above the pretreatment serum PSA baseline. Time to treatment failure was the time between randomization and any of the aforementioned end points. Time to disease progression was defined as the time between randomization and disease progression or death.

QOL Assessment

QOL assessments were to be conducted at study entry, at 6 and 12 weeks after study entry, and then at 12-week intervals. A QOL assessment was also planned for the time of treatment failure. The baseline assessment was completed while the patient was in the clinic. Follow-up interviews were conducted by telephone under the direction of the QOL study coordinator.

Five QOL assessments were used. The Functional Living Index–Cancer (FLIC) is a 22-item questionnaire with each item scored from 1 to 7.[11] Subscales of this instrument include physical well-being (12 items), emotional state (five items), and family disruption (two items). The FLIC was used to provide a global assessment of QOL. The Symptom Distress Scale includes 11 items, each of which is scored

from 1 to 5.[12] Specific items include assessments of appetite and fatigue and two assessments of pain (how often and how severe). This scale was used to provide an in-depth evaluation of cancer-related symptoms. The Sexual and Urologic Functioning scale includes seven items taken from the European Organization for the Research and Treatment of Cancer Prostate Cancer Patients' QOL Questionnaire.[13] Three of the items address sexual functioning, and four items address urologic functioning. All seven items are scored from 1 to 4. The Problems in Daily Activities scale consists of eight items scored from 1 to 5.[14] This scale was intended to provide a detailed evaluation of problems in everyday activities. The Impact of Pain on Daily Activities instrument contains seven items that ask the patient to rate, on a scale from 0 to 10, the impact that their pain has on activities such as sleep and normal work.[15]

RESULTS

Table 1 lists the characteristics of the 242 patients at baseline. The median age of patients on this study was 72 years, 91% of the patients were white, the median length of time since diagnosis was 3.3 years, and median serum PSA level at study entry was 150 ng/mL. More than 90% of patients had bone metastases, and 85% of patients had a CALGB performance status of 0 or 1. There were no significant differences between the two treatment arms with respect to baseline clinical characteristics other than prior treatment with a progestational agent. Hydrocortisone was continued in all patients until disease progression or treatment failure. Its continuation was encouraged in both treatment arms until death. The median number of cycles of mitoxantrone administered was five.

The main objective of this study was to compare the survival duration of hydrocortisone alone versus M+H. Figure 1 shows that there was no difference in survival between the treatment arms (median duration, 12.6 months for hydrocortisone *v* 12.3 months for M+H; log-rank test = .08, 1 df, $P = .77$). There was a small but statistically significant difference favoring M+H with respect to time to disease progression (Fig 2) and time to treatment failure (data not shown). Treatment failure and disease progression occurred at a median time of 2.3 months after initiation with hydrocortisone alone compared with a median 3.7 months with M+H (log-rank, $P = .0254$ for treatment failure and $P = .0218$ for disease progression).

There were 29 patients (31%) in the M+H arm who progressed according to the measurable disease criteria compared with 28 patients (27%) in the hydrocortisone-alone arm. Sixty-six patients (69%) in the M+H arm progressed according to the bone scan compared with 77 (71%) in the hydrocortisone-alone arm. Progression as measured by PSA included 54 patients (57%) in the M+H compared with 48 (46%) in the hydrocortisone-alone arm. Progression according to performance status included 38 patients (39%) in the M+H arm versus 42 (39%) in the hydrocortisone-alone arm.

Table 1. Baseline Characteristics by Treatment Arm

	M + H		Hydrocortisone Only		
	%	No. of Patients*	%	No. of Patients*	P
Demographics					
Age, years					
Median	72	119	72	123	.548
Interquartile range	67-75		65-75		
White race	88	119	93	123	.238
Metastases†					
Bone	91	119	90	123	.892
Lymph node involvement	21	117	17	121	.238
Lung	9	117	9	121	.957
Liver	9	117	16	110	.610
Years since diagnosis					
Median	3.3	111	3.4	110	.402
Interquartile range	1.9-6.3		1.9-5.2		
Laboratory values					
Hemoglobin, g/dL					
Median	11.9	119	12.4	123	.272
Interquartile range	11-13		11-13		
PSA, ng/mL					
Median	150	119	141	123	.884
Interquartile range	52-362		54-416		
Alkaline Phosphatase, IU/L					
Median	167	113	163	116	.992
Interquartile range	105-317		104-369		
Creatinine, mg/dL					
Median	1.1	119	1.1	123	.835
Interquartile range	0.9-1.3		0.9-1.3		
Prior therapy‡					
Surgical Castration	59	116	61	123	.715
Estrogen	8	115	13	121	.246
LHRH analog	47	117	45	121	.713
Progesterone agent	7	115	18	121	.010
Antiandrogen	69	116	75	122	.267
QOL					
Performance status of 0 or 1	85	119	88	122	.328
No analgesic use	35	118	40	120	.884

Abbreviation: LHRH, luteinizing hormone–releasing hormone.
*Number of patients evaluated on the characteristic.
†Patient may have more than one metastasis.
‡Patient may have more than one type of prior therapy.

Table 2 summarizes the best response by treatment arm as defined in Patients and Methods. This analysis is based on 234 eligible patients who received study treatment. Only 69 patients were considered to have measurable disease. No CRs were observed in either treatment arm. PRs were observed in eight (7%) of 116 patients who received M+H and in five (4%) of 118 who received hydrocortisone alone. There was no significant difference in the CR + PR rates between arms (χ^2 test = .788; 1 df; $P = .375$). Stable disease was more common with M+H (65 of 116; 56%) versus hydrocortisone alone (50 of 118; 42%). A post hoc analysis showed that 73 (64%) of 116 patients had either a CR, a PR, or stable disease with M+H compared with 55 (47%) of 118 with hydrocortisone alone (χ^2 test = 6.29, 1 df, $P = .012$).

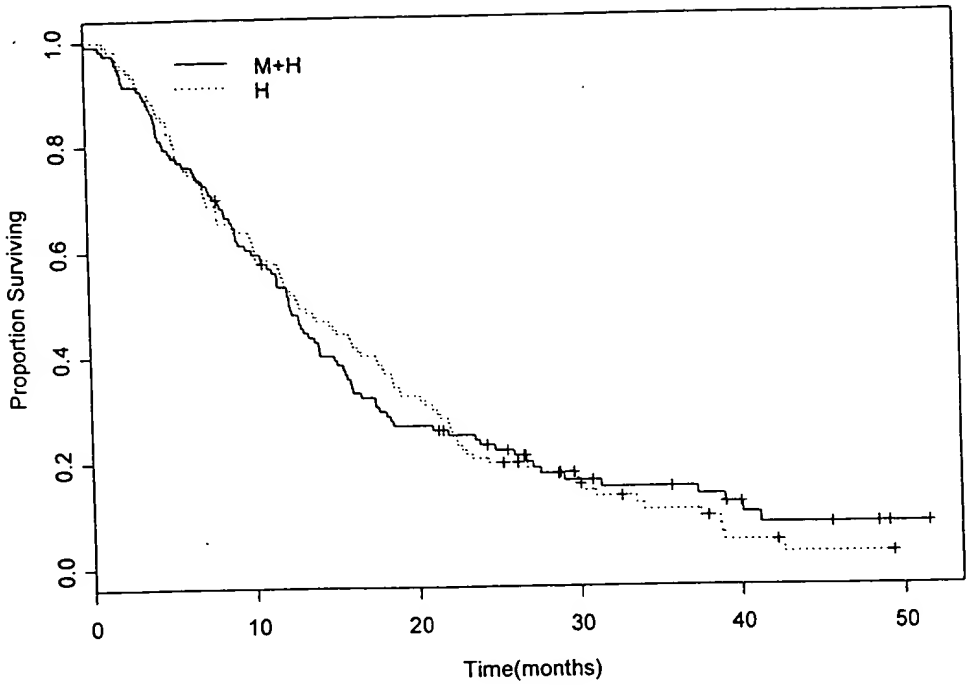

Fig 1. Overall survival.

There were 1,704 serum PSA measurements, 242 measurements at study entry, and 1,462 after baseline. Of the postbaseline measurements, 849 were in the M+H arm and 613 in the hydrocortisone-alone arm. There were 161 serum PSA measurements after 12 months: 97 in the M+H arm and 64 in the hydrocortisone-alone arm. Table 3 summarizes decrease in serum PSA by treatment arm. The protocol mandated a serum PSA evaluation between 28 and 56 days after initiation of treatment. When the 187 patients who had serum PSA measurements between 28 and 56 days were analyzed, 13 (14%) of 81 patients treated with hydrocortisone alone achieved a ≥ 50% decrease in serum PSA compared with 18 (19%) of 96 patients treated with M+H. The difference was not statistically significant (χ^2 = .67; 1 df; P = .412). Similarly, four patients treated with hydrocortisone alone achieved a ≥ 80% decrease in serum PSA compared with four patients treated with M+H.

A post hoc analysis showed that 42 (38%) of 112 patients who received M+H achieved a maximum serum PSA decrease of ≥ 50% compared with 25 (22%) of 116 patients who received hydrocortisone alone (χ^2 = .985; 1 df; P = .008). A maximum serum PSA decrease of ≥ 80% was achieved in 22 (20%) of 112 patients who received M+H compared with 11(9.0%) of 116 patients who received hydrocortisone alone (χ^2 = 4.752, 1 df, P = .029; Table 3). The discrepancy between the response rates determined before as opposed to after 56 days reflects the fact that most patients who had a decrease in serum PSA level to ≥ 50% or more than 80% did so beyond 56 days after initiation of treatment. Survival by maximum postbaseline serum PSA decrease is shown in Figure 3. Patients who achieved a ≥ 50% or a ≥ 80% decline from baseline in both cases had a median survival duration of 20.5 months, which was 10.3 months longer than those who did not (log-rank, $P < .001$).

Table 4 shows the pretreatment factors that were significant for prediction of survival duration. These factors included baseline lactate dehydrogenase level (≥ 227 U/L v < 227 U/L; hazards ratio = 1.5), baseline hemoglobin level (> 13 g/dL v < 13 g/dL; hazards ratio = 0.7), baseline alkaline phosphatase level (≥ 165 U/L v < 165 U/L; hazards ratio = 1.7), and baseline serum PSA level (≥ 150 ng/mL v < 150 ng/mL; hazards ratio = 1.4). Although performance status and weight loss were significant predictors in univariate analysis, they were not significant predictors in multivariate analysis. Age, race, treatment arm, measurable disease, previous surgery, previous radiotherapy, previous surgery, previous orchiectomy, and number of prior endocrine manipulations all proved insignificant.

Of the 234 eligible patients who started treatment, 196 (84%) completed at least one of the five QOL instruments at baseline, and 183 patients (78%) completed at least one instrument after baseline. A total of 155 patients (66%) were assessed at baseline and at least one follow-up examination. Of the 51 patients who did not have a postbaseline QOL assessment, five died and two had withdrawn consent before the first scheduled QOL assessment at 6 weeks. When patients who did not fill out at least one follow-up questionnaire were compared with those who did, there were significant differences in baseline characteristics. Those who did not complete a follow-up questionnaire had, on average,

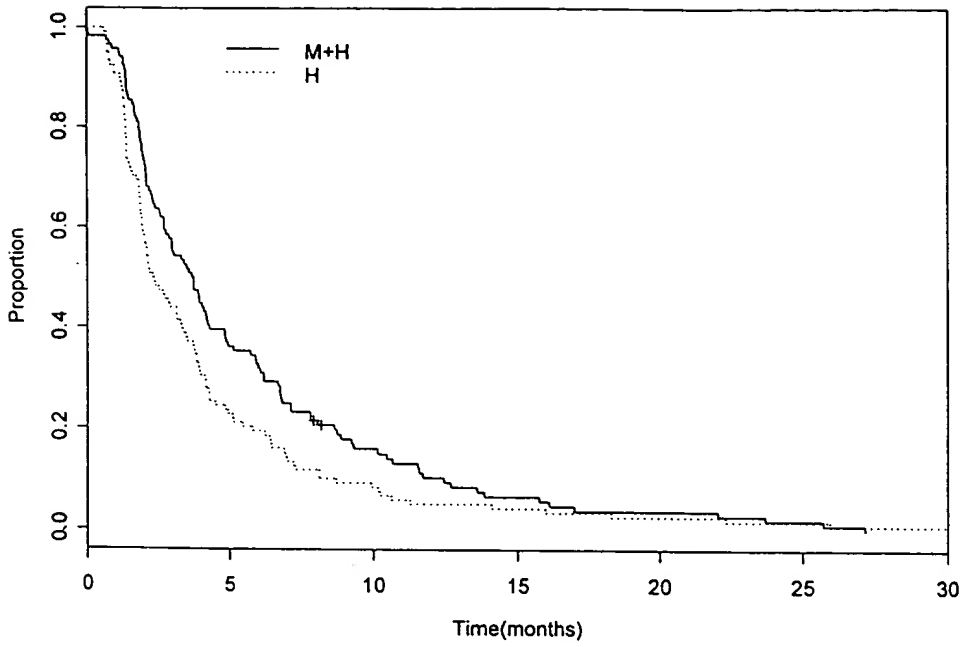

Fig 2. Time to progression.

a poorer performance status and lower QOL scores (as measured by the FLIC). In a multivariate regression analysis, QOL was analyzed in patients who completed a baseline assessment and at least one follow-up assessment. Table 5 summarizes the results of the QOL measures based on estimates of the mean postbaseline average score between treatment groups, adjusting for stratification factors and the baseline score. There were no statistically significant differences between the two arms in a variety of QOL measures, including global QOL (as measured by the total FLIC score), sexual and urologic function, problems of daily activity, and the summary score of the impact of pain scale. However, there was an indication of better QOL in the M+H arm as measured by favorable responses to individual questions and subscales. The differences in the FLIC emotional state subscale (P = .04), FLIC family disruption subscale (P = .02), and two pain items from the symptom distress scale (how often [P =.06] and how severe [P =.03]) all favored the M+H arm. However, the symptom distress scale total and the sexual and urologic function total favored the hydrocortisone-alone arm.

There were no reported treatment-related deaths. The most commonly reported grade 3 and 4 toxicities were hematopoietic toxicity in approximately 70% of patients in the M+H arm (Table 6). The difference between the two arms with regard to hematopoietic toxicity was statistically significant. Cardiac toxicity is a concern with mitoxantrone. We found the rate of grade 3 and 4 cardiac dysfunction to be higher (5%) with M+H than with hydrocortisone alone (0%), but this was not statistically significant. No deaths were attributed to M+H-induced cardiac toxicity.

DISCUSSION

The results of this study indicate that M+H is more active than hydrocortisone alone, as demonstrated by more frequent decreases in serum PSA levels and a longer time to

Table 2. Greater Than 50% and 80% Reduction in PSA from Baseline at 28 to 56 Days by Arm

PSA Response (%)	Treatment Arm: M + H No.	M + H %	Hydrocordisone Alone No.	Hydrocordisone Alone %	Total No.	Total %
< 50	78	81.3	78	85.7	156	83.4
≥ 50*	18	18.7	13	14.3	31	16.6
≥ 80*	4	4.2	4	4.3	8	4.3

*The rows ≥ 50% and ≥ 80% are not mutually exclusive; therefore, the number of patients with a PSA response ≥ 50% includes those whose response was ≥ 80%.

Table 3. Greater Than 50% and 80% Reduction in PSA From Baseline by Arm

PSA Response (%)	Treatment Arm: M + H No.	M + H %	Hydrocordisone Alone No.	Hydrocordisone Alone %	Total No.	Total %
< 50	70	62.5	91	78.5	161	70.6
≥ 50*	42	37.5	25	21.5	67	29.4
≥ 80*	22	19.6	11	9.5	33	14.5

*The rows > 50% and ≥ 80% are not mutually exclusive; therefore, the number of patients with a PSA response > 50% includes those whose response was ≥ 80%.

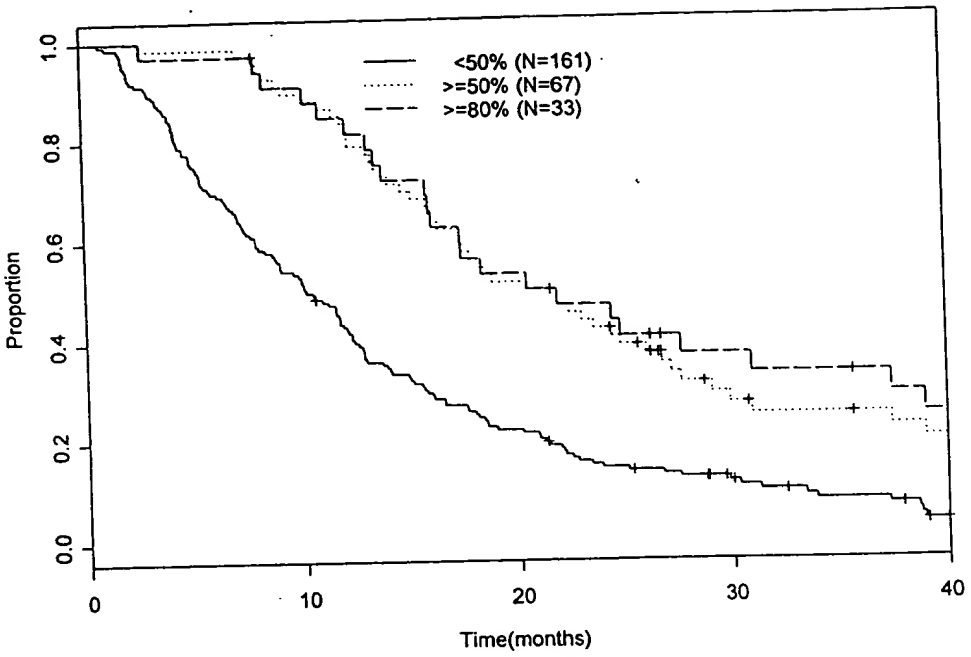

Fig 3. Survival by PSA reduction (n = 228). PSA reduction groups are not mutually exclusive.

treatment failure. However, this difference did not result in a significant improvement in survival, the primary end point of this study. The power calculations for this study were based on an anticipated 12-month survival for the hydrocortisone-alone arm and an expectation that M+H might improve survival by 50%. The estimate of 12-month median survival was correct. Although the 50% improvement in survival might be viewed as an overly optimistic expectation, the decision by the investigators was that a clinically meaningful change in survival for this population would be a 50% improvement in survival. Sensitivity analysis indicated that it is unlikely that a small (> 10%) improvement in survival was missed (data not shown). We believe the primary reason for this is that mitoxantrone lacks sufficient activity in HRPC to translate into a survival benefit. An additional explanation may be that the use of other treatments after treatment failure conceivably could have muted any survival impact of mitoxantrone. This study did not address the potential utility of mitoxantrone in patients with earlier disease, nor did it address the possibility that other drugs or combination chemotherapy with or without mitoxantrone might improve survival in patients with HRPC.

The results of this study support the use of M+H as a palliative combination in HRPC. Tannock et al[5] demonstrated the added benefit of mitoxantrone plus prednisone over prednisone alone in patients with symptomatic HRPC. In their study, the effect of treatment on pain, analgesic use, and QOL were the primary end points, whereas in our study,

Table 4. Estimates of the Prognostic Factors of Survival From the Proportional Hazards Model

Variable	Hazards Ratio	95% Confidence Limits	P
Alkaline phosphatase ≥ 165 U/L v < 165 U/L	1.70	1.3, 2.3	< .001
Lactate dehydrogenase ≥ 227 U/L v < 227 U/L	1.50	1.2, 2.0	.003
Hemoglobin > 13 g/dL v < 13 g/dL	0.70	0.5, 0.9	.021
Baseline PSA ≥ 150 ng/mL v < 150 ng/mL	1.40	1.1, 1.8	.045
Treatment arm, M + H v hydrocortisone alone	1.0	0.8, 1.3	.976

Table 5. Estimated Treatment Effects, Adjusting for Baseline Score and Stratification Factors

QOL Outcome	Estimated Difference*	SE	P
FLIC: total	− 4.34	2.74	.12
Symptom distress: total	0.05	0.92	.96
Sexual and urological function: total	0.08	0.57	.89
Problems in daily life: total	− 1.25	0.97	.20
Impact of pain: total	− 1.87	2.12	.38
FLIC: physical well-being	− 1.90	1.79	.29
FLIC: emotional state	− 1.42	0.69	.04
FLIC: family disruption	− 0.93	0.39	.02
FLIC item: pain from cancer	0.35	0.31	.26
FLIC item: pain interferes	− 0.18	0.22	.43
Symptom distress item: pain, how often	− 0.30	0.15	.06
Symptom distress item: pain, how severe	− 0.28	0.13	.03
Symptom distress item: appetite	0.08	0.14	.59
Symptom distress item: fatigue	− 0.06	0.14	.68

*Coefficient of indicator for treatment effect: 1 for M + H, 0 for hydrocortisone only. Negative values indicate better QOL with M + H; positive values are in favor of the hydrocortisone-only group.

Table 6. Percentage of Patients with Grade 3 and Greater for Specific Toxicities

Toxicity	Treatment Arm: M + H %	M + H No.†	Hydrocortisone Only %	Hydrocortisone Only No.	P‡
WBC	59	112	1	113	< .001
Platelets	6	112	0	112	< .01
Granulocytes/bands	63	112	1	113	< .001
Lymphocytes	70	110	15	111	< .001

*Percentage of patients within treatment arm with grade 3 or 4 toxicity.
†Number of patients within treatment arm evaluated for the toxicity.
‡Fisher's exact test.

survival was the primary end point. The present study did not demonstrate as robust an improvement of QOL in the M+H arm, although there were elements similar to the study by Tannock et al that favored the M+H arm, specifically, the frequency and severity of pain. Three potential explanations for the difference between our results and the results of Tannock et al are that more than one third of patients in our study at baseline either had no pain or pain that was not sufficient to warrant pain medication, whereas in the study by Tannock et al, pain was a prerequisite. Second, there was a high (34%) dropout rate with regard to assessment of QOL parameters. Both of these factors may have compromised the power to measure a difference in QOL between treatment arms. Finally, the instrument used for measuring QOL in the study by Tannock et al may have been more sensitive than the instruments used in our study. Nonetheless, the results of our study generally support a benefit with respect to pain control of M+H over hydrocortisone alone.

The present study represents one of the largest randomized chemotherapy trial in which an assessment of prognostic factors could be made. The results support the observations of others that baseline lactate dehydrogenase, alkaline phosphatase, hemoglobin, and PSA levels at baseline are predictive of survival outcome.[16-25]

The results of the analysis of PSA decreases is intriguing. First, maximum PSA decreases were achieved slowly, usually after 2 months of therapy. The difference in the two treatment arms with regard to frequency of decline could only be appreciated after this interval of time. Second, a $\geq$ 50% decrease in PSA was associated with a longer survival, supporting the observations of other studies that this may be a clinically meaningful end point in patients with HRPC.[21-23] And finally, no difference in survival was observed in patients who achieved a $\geq$ 80% decrease over those who achieved a $\geq$ 50% decrease, suggesting that this more rigorous criterion of activity adds no further clinical information than that which is demonstrated by a $\geq$ 50% decrease.

Finally, the toxicity observed in this study was very modest, particularly considering the age of the patients. Although there was a high frequency of grade 3 or 4 hematopoietic toxicity in the M+H arm, this did not result in undue morbidity. Neutropenic fevers were unusual, even with the stipulation that growth factor support was discouraged. Given the potential cardiac toxicity of mitoxantrone, it is encouraging that cardiac dysfunction was rarely reported, although exclusively, in the M+H arm. The probable reasons for this are that cardiac function was monitored closely with serial studies and that few patients received large cumulative doses of mitoxantrone.

In conclusion, M+H is beneficial to a proportion of patients with HRPC, and this combination may be used as a control arm in future phase III trials. However, new drugs and combination regimens, as well as novel therapeutic strategies, are needed.

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